

1 **Compositions and Uses Thereof**

2

3 **Field of the Invention**

4

5 The present invention relates to methods of
6 controlling serum glucose levels in mammals. In
7 particular it relates to methods for the prevention
8 of severe fluctuations in glucose levels and the use
9 of these methods in the treatment of diseases
10 characterised by hypoglycaemia, such as glycogen
11 storage disease (GSD), clinical conditions where a
12 slow release of energy in the form of glucose may be
13 required (e.g. diabetes) and for sports and fitness
14 type products where a slow release of energy is
15 desirable.

16

17 **Background to the Invention**

18

19 The release of energy from foods and food products
20 is a complex process. It depends on the composition,
21 structure, extent of modification and volume of the
22 food. Apart from this, it is also variable between

1 individuals and reflects many different factors
2 which probably include a combination of age, level
3 of fitness, rate of gastric emptying and
4 peristalsis, sex, size, state of health etc. Energy
5 may be derived from different food sources, for
6 example, carbohydrates, lipids and proteins, alcohol
7 etc. In many animals, including man, energy is
8 stored as fat (adipose tissue) and provides a
9 reserve when food is limiting. There is a more
10 readily available form of energy, however, where a
11 glucose polymer (glycogen) is stored in muscles and
12 the liver and can be rapidly mobilised when
13 required. The formation and storage of glycogen is a
14 synchronised enzymatic process which is controlled
15 in part by insulin which promotes the formation of
16 glycogen from the glucose precursors (Figure 1).
17 Glucose deposition and glycogen catabolism is co-
18 ordinated in man to maintain blood glucose at
19 $\sim 4.5 \text{ mmol l}^{-1}$.

20

21 *Glycogen storage disease*

22

23 In the normal human, the anabolism and catabolism of
24 glycogen is normally co-ordinated and regulated. The
25 deposition of glycogen is promoted by insulin whilst
26 the hydrolysis of glycogen and conversion to glucose
27 is promoted by adrenaline (especially muscle) and
28 glucagons (especially liver).

29

30 In glycogen storage disease (GSD) there is an
31 inherited defect with respect to the deposition or
32 hydrolysis of glycogen

1 <http://www.agisd.org.uk/home/information.asp>;
2 http://agsdus.org/body_what1s_1.html) and
3 consequently the concentration of blood glucose.
4 Figure 1 outlines the principles of glycogen
5 metabolism.

6
7 The most common types of glycogen storage disease
8 are:

9
10 In Type I (Von Gierke Disease) individuals suffer
11 from a lack of glucose-6-phosphatase activity ('h'
12 in Figure 1) and hence cannot generate glucose from
13 glycogen. Consequently they need to be tube fed to
14 maintain blood glucose.

15 In Type II (Pompe's Disease) individuals suffer
16 from a lack of α -glucosidase activity ('i' in Figure
17 1). Infants often die of this form very young.

18 In Type III (Cori's Disease) individuals suffer
19 from a lack of debranching enzyme activity ('i' in
20 Figure 1). Treatment usually consists of a high
21 protein diet.

22 In Type IV (Anderson's Disease) individuals
23 suffer from a lack of branching enzyme activity ('e'
24 in Figure 1). Liver transplantation is the only
25 viable therapy.

26 In Type V (McArdle's Disease) individuals suffer
27 from a lack of muscle phosphorylase activity ('f' in
28 Figure 1). Extensive exercise should be avoided.

29 In Type VI (Her's Disease) individuals suffer
30 from a lack of liver phosphorylase activity ('f' in
31 Figure 1). There is a male X- chromosome link.

1 In Type VII (Tarui's Disease) individuals suffer
2 from a lack of muscle phosphofructokinase activity.
3 Extensive exercise should be avoided.

4 In Type IX individuals suffer from a lack of
5 liver phosphorylase activity ('f' in Figure 1).
6 There is a male X- chromosome link and it is
7 comparable to type VI.

8
9 Low blood glucose can be treated by the slow
10 administration of glucose (oral or intra-venous), or
11 from starch hydrolysates (e.g. maltose, dextrans
12 etc.) or from native starch where glucose is
13 liberated as a consequence of digestion. In practice
14 'corn-starch', which is normal maize starch, is used
15 to treat glycogen storage disease (especially during
16 sleep) due to availability and to lack of a superior
17 alternative in terms of digestive response. The
18 starch must be slowly digested and not converted to
19 glucose rapidly or excreted with little hydrolysis.
20 In other clinical conditions (such as diabetes
21 mellitus) there is also the need to supply glucose
22 slowly and from a non-sugar based matrix (e.g.
23 cakes, biscuits, sweets etc.). This can, therefore,
24 also be achieved by starch (hydrolysis in the gut)
25 and is important for night time regimes where
26 glucose is essential in the blood but within a
27 controlled form.

28
29 The advantages and disadvantages of feeding glucose,
30 maltodextrins or maize starch for clinical nutrition
31 with a perceived optimal substrate are defined in
32 Table 1.

1

2 Table 1. Release profile of glucose based substrates
 3 in the gut of man with perceived optimised product
 4 in this respect

5

Entry to body	Glucose	Maltodextrin	Normal maize (<i>'corn'</i>) starch	
Intravenous	Used extensively in medicine. Would need to be pumped constantly for GSD and diabetes clinical maintenance.	Too high molecular weight	Inappropriat e in view of size, composition and structure	Appropriate in view of size, composition and structure
Oral - small intestine	Rapidly absorbed (1.5 hours)	Rapidly absorbed (1.5 hours)	Glucose released within 4 hours	Glucose released over 7.5 hours (to provide overnight release)
Oral - large intestine	Not applicable	Not applicable	Possibly mostly digested with small amount of fermentable substrate	Minimal fermentable substrate to avoid loss of energy and fermentation

6

7 *Slow release of energy*

8

9 Apart for the clinical conditions described above,
 10 athletes require sustained release of energy. There

1 are many products on the market which release energy
 2 based on sugars or maltodextrins. These include
 3 products presented in Table 2. However, sugars and
 4 dextrans are absorbed very rapidly and these
 5 products must be consumed regularly to maintain the
 6 required body loading of the energy.

7

8 Table 2. Energy based products currently found on
 9 the market.

10

Product	Carbohydrate, % of product	Carbohydrates used as energy source
Accelerade	7.75	Fructose, maltodextrin and sucrose
Allsport	9.00	High fructose syrup
Cytomax	6.00	High fructose syrup and maltodextrin
Enervit G	7.60	Fructose, glucose, maltodextrin and sucrose
Extran thirstquencher	5.00	Fructose and maltodextrin
G Push	7.50	Fructose, galactose and maltodextrin
Gatorade	6.00	Fructose, glucose and sucrose
GU20	5.70	Fructose and maltodextrin
Powerade	8.00	High fructose syrup and glucose polymers [sic]
Revenge Sport	7.00	Fructose, glucose and maltodextrin

11 (adapted from [www.accelerade.com/accelerade-](http://www.accelerade.com/accelerade-comparison-results.asp)
 12 [comparison-results.asp](http://www.accelerade.com/accelerade-comparison-results.asp))

1

2

3 *Slow energy release nutritional formulations*

4

5 As mentioned above, slow release products for sports
6 nutrition tend to be pouched relying on glucose or
7 maltodextrin to supply the energy. These actually
8 are absorbed quickly as they are either readily
9 absorbed (e.g. glucose) or converted to glucose
10 relatively rapidly (e.g. maltodextrins, probably
11 within 60 minutes maximum).

12

13 On the other hand, glycogen storage disease (certain
14 treatable forms, see above) management requires that
15 patients receive a slow release of glucose,
16 especially, for example, overnight. Native starch is
17 provided for this purpose where: the initial
18 liberation phase of glucose is not too rapid (see
19 figures below); glucose is released at as constant a
20 rate as possible which must not be too slow or too
21 fast and; the production of lactate (anaerobic
22 respiration) is minimised. Certain starches are to
23 be avoided as they exhibit only limited hydrolysis
24 in the native form (e.g. potato).

25

26 Hence, the extent and rate of starch digestion are
27 important parameters with respect to glucose release
28 from the ingested α -glucan. Regulation in terms of
29 these parameters reflect the state of the starch and
30 the rate at which the energy source travels through
31 the gut. A balance in terms of energy release is

1 required which can be controlled by the energy
2 source and the transit time.

3
4 Osmolality is also an important feature with respect
5 to carbohydrate usage. Sugar solutions exert a high
6 osmotic pressure compared to polysaccharides due to
7 the number of moles in solution.

8
9 The viscosity of the consumed material will also
10 affect the capacity for it to be hydrolysed and to
11 permit associated compounds to come into contact
12 with the mucosal surface. This is a very important
13 issue with respect to product development regarding
14 potential energy sources.

15
16 Glycaemic Index (GI) is also an important
17 determinant of energy availability from foods and
18 more especially α -glucans. In this context, white
19 bread has a GI of 1 which is the same as pure
20 glucose and represents one hundred percent
21 availability of the α -glucan fraction (or 1 on a
22 scale from 0 to 1).

23
24 *Gastric emptying*

25
26 As mentioned above, the rate and extent of gastric
27 emptying will in part regulate the transit time of
28 food materials through the gut. It is established
29 that high volumes - low energy promote gastric
30 emptying whereas low volumes - high energy restrict
31 gastric emptying. Lipids and proteins are valuable

1 aids with respect to restricting emptying of the
2 stomach.

3
4 Glycogen storage disease and diabetes are
5 classically managed by feeding 'cornstarch' which is
6 normal maize starch (Kaufman, 2002). Sometimes,
7 proportions of carbohydrates are utilised which
8 provide rapid (e.g. sugar), medium (e.g. gelatinised
9 starch) and slow ('cornstarch') digestion and hence
10 glucose appearance in the blood (Wilbert, 1998).
11 Sugar combinations with or without maltodextrins or
12 'glucose polymers' are often employed in 'energy
13 drinks' (including rehydration drinks) and often
14 with other components like salts, protein, fatty
15 acids, glycerol, minerals, flavouring etc. (Gawen,
16 1981; Tauder et al, 1986; Burling et al, 1989;
17 Gordeladze, 1997; Paul and Ashmead, 1993 and 1994;
18 Vinci et al, 1993; Fischer et al, 1994; Simone,
19 1995; Gordeladze, 1997; King, 1998; Kurppa, 1998;
20 Cooper et al, 2001; Portman, 2002). The
21 maltodextrins/ glucose polymers are used to slow
22 energy availability (compared to sugars) and exert
23 less osmotic pressure.

24
25 Brynolf et al (1999) describe the production of an
26 acid modified starch with a molecular weight of
27 15,000 to 10,000,000 produced by classical acid
28 hydrolysis of starch to be used as an energy source
29 prior to physical activity. Lapré et al (1996) have
30 discussed the option of coating food with non-starch
31 polysaccharides (cation gelling) to reduce the
32 glycaemic response of carbohydrate containing foods.

1
2 However, although currently available starch
3 preparations used in the treatment of conditions
4 such as GSD have prolonged glucose release profiles
5 compared to glucose and maltodextrin based products,
6 the time period over which the products enable serum
7 glucose levels to be maintained within an acceptable
8 range is relatively short. Thus, at present, using
9 conventional oral preparations, patients susceptible
10 to hypoglycaemic episodes generally must ingest such
11 glucose sources at intervals of no longer than 4
12 hours. Although this may be acceptable during
13 daytime, the need for repeated feeding is very
14 inconvenient at nighttime. The patient thus must
15 either awake or be wakened overnight to feed or,
16 alternatively, sleep with a nasogastric tube in
17 place to provide a constant source of glucose.

18
19 Accordingly, there is a great need for alternative
20 means of maintaining serum glucose levels within
21 safe ranges over a longer period of time than that
22 afforded by the conventional treatments.

23
24 Summary of the Invention

25
26 The present inventors, after considerable work, have
27 surprisingly discovered that semi-crystalline waxy
28 starches afford significantly prolonged glucose
29 release in the human GI tract compared to normal or
30 high amylose semi-crystalline starches as
31 conventionally used in preparations for slow energy

1 release.

2

3 Accordingly, in a first aspect, the present
4 invention provides a method of controlling serum
5 glucose levels in an individual said method
6 including the step of administering to said
7 individual a therapeutic food composition comprising
8 a waxy starch.

9

10 In a second aspect, the invention provides a method
11 of treating or preventing hypoglycaemia in an
12 individual said method including the step of
13 administering to said individual a therapeutic food
14 composition comprising a waxy starch.

15

16 According to a third aspect, the invention provides
17 a method of treating an individual susceptible to
18 hypoglycaemic episodes, said method including the
19 step of administering to said individual a
20 therapeutic food composition comprising a waxy
21 starch.

22

23 In one preferred embodiment, said treatment is
24 treatment to prevent or decrease night-time
25 hypoglycaemic episode(s).

26

27 As described herein, the inventors have found that
28 waxy starches provide prolonged glucose release when
29 ingested.

30

31 Moreover, as well as discovering that such semi-
32 crystalline starches provide advantageous slow

1 glucose release, the inventors have unexpectedly
2 found that the time period over which glucose may be
3 released from starches and thus the time period over
4 which serum glucose levels may be maintained in
5 patients without the need for further doses of food
6 compositions can be markedly increased by
7 hydrothermal treatment of starches for use in the
8 invention. Indeed, as demonstrated in the Examples
9 below, the time period over which serum glucose
10 levels may be maintained in patients without the
11 need for further doses of food compositions may be
12 prolonged by use of such hydrothermally treated
13 starches (for example heat moisture treated
14 starches) to more than six hours, indeed typically
15 more than 7 hours. Thus, the use of such starches
16 (or indeed other hydrothermally treated starches) in
17 the methods of the invention enables a patient
18 susceptible to night-time hypoglycaemic episodes to
19 sleep for a substantially normal duration i.e. more
20 than 6 hours, preferably more than 7 hours, without
21 the need for nasogastric feeding or further food
22 doses throughout the night.

23
24 Accordingly, in preferred embodiments of the
25 invention, the starch is hydrothermally treated
26 (HTT) waxy starch. Preferably said hydrothermally
27 treated waxy starch is heat-moisture treated (HMT)
28 waxy starch.

29

30 However, as well as finding that hydrothermal
31 treatment has very advantageous effects on waxy
32 starches, the inventors have also shown that

1 hydrothermal treatment also improves and prolongs
2 the glucose release profile of non-waxy starches.

3
4 Accordingly, in a fourth independent aspect of the
5 present invention, there is provided a method of
6 controlling serum glucose levels in an individual
7 said method including the step of administering to
8 said individual a therapeutic food composition
9 comprising a hydrothermally treated starch.

10

11 In a fifth aspect, the invention provides a method
12 of treating or preventing hypoglycaemia in an
13 individual said method including the step of
14 administering to said individual a therapeutic food
15 composition comprising a hydrothermally treated
16 starch.

17

18 According to a sixth aspect, the invention provides
19 a method of treating an individual susceptible to
20 hypoglycaemic episodes to prevent or decrease
21 hypoglycaemic episode(s), said method including the
22 step of administering to said individual a
23 therapeutic food composition comprising
24 hydrothermally treated starch.

25

26 In one preferred embodiment, said treatment is
27 treatment to prevent or decrease night-time
28 hypoglycaemic episode(s).

29

30 In the fourth, fifth and sixth aspects of the
31 invention, any suitable hydrothermally treated
32 starch may be used. Said hydrothermally treated

1 starch may be starch which has been heat moisture
2 treated or starch which has been subjected to
3 annealing treatment. In preferred embodiments the
4 hydrothermally treated starch is heat moisture
5 treated starch.

6

7 In preferred embodiments of the invention, starch of
8 and for use in the invention is a "waxy starch".

9

10 Waxy starches for use in any aspect of the present
11 invention may be any starch having an amylopectin
12 content of at least 70%, preferably at least 80%,
13 more preferably at least 85%, even more preferably
14 at least 90%, yet more preferably at least 95%, most
15 preferably at least 98% amylopectin. Such waxy
16 starches may be cereal or non-cereal waxy starches.
17 Preferably, said waxy starch is a waxy cereal
18 starch, for example waxy maize starch.

19

20 Preferably, the starch of and for use in the
21 invention should have a granular size in the range
22 10 to 35 μ m, more preferably in the range 15 to 30 μ m.

23

24 Preferably the starch used in the invention enables
25 a blood glucose concentration of greater than 3.0
26 mmol l⁻¹ at 300 min post administration.

27

28 In preferred embodiments, the therapeutic food
29 composition is such that it, in use, its
30 administration results in a maximum blood glucose
31 concentration of no greater than 9 mmol l⁻¹. In a
32 further embodiment, in use, administration of the

1 therapeutic food composition results in a maximum
2 blood glucose concentration of no greater than 8
3 mmol l⁻¹.

4
5 In particularly preferred embodiments, the starch,
6 in use, enables a blood glucose concentration of
7 greater than 3.0 mmol l⁻¹ at 300 min post
8 administration, but does not cause a peak in blood
9 glucose concentration of any greater than 9.0 mmol
10 l⁻¹, for example not greater than 8.0 mmol l⁻¹

11
12 References to blood glucose concentration relate to
13 a typical adult human of normal weight, for example
14 72 kg.

15
16 Preferably therapeutic food compositions of and for
17 use in the method of the present invention comprise
18 per unit dose greater than 50g, preferably greater
19 than 60g , for example more than 70g, even more
20 preferably greater than 80g, most preferably at
21 least 90g of the starch.

22
23 In a seventh aspect of the invention, there is
24 provided the use of a starch in the preparation of a
25 therapeutic foodstuff for the treatment of
26 hypoglycaemia, wherein said starch is a waxy and/or
27 hydrothermally treated starch.

28
29 Also provided by the invention is the use of starch
30 in the preparation of a therapeutic foodstuff for
31 the treatment or prevention of hypoglycaemic
32 episode(s), for example night-time hypoglycaemic

1 episode(s), wherein said starch is a waxy and/or
2 hydrothermally treated starch.

3

4 Further provided by the invention is a therapeutic
5 foodstuff comprising a starch, wherein said starch
6 is a waxy and/or hydrothermally treated starch.

7

8 Therapeutic foodstuffs and food compositions of and
9 for use in the invention may be provided in kit
10 form. Accordingly, in a eighth aspect, the
11 invention provides a therapeutic food kit, said food
12 kit comprising:

- 13 a) a therapeutic food composition comprising starch,
14 wherein said starch is a waxy and/or hydrothermally
15 treated starch; and
16 b) instructions for ingesting said therapeutic food
17 composition.

18

19 The methods and therapeutic foodstuffs of and for
20 use in the invention may be used to treat
21 individuals with any disease associated with the
22 presence or susceptibility to hypoglycaemia. Such
23 diseases include, but are not limited to diabetes
24 (Type I or Type II), glycogen storage disease, liver
25 disease, for example, liver cirrhosis.

26

27 Moreover the methods and therapeutic foodstuffs of
28 and for use in the invention are not limited to use
29 with individuals having such disease. The
30 demonstration by the present inventors that
31 starches, which are waxy and/or hydrothermally
32 treated, afford significantly prolonged glucose

1 release in the GI tract compared to normal starches
2 enables the use of such waxy and/or hydrothermally
3 treated starches in therapeutic foodstuffs for
4 sports nutrition, for example, to provide a
5 sustained release food source during exercise, for
6 example, prolonged exercise.

7
8 Accordingly, the invention further extends to the
9 use of a starch in the preparation of sports
10 nutrition foodstuff, wherein said starch is a waxy
11 and/or hydrothermally treated starch.

12
13 Further provided by the invention is a sports
14 nutrition foodstuff comprising a starch, wherein
15 said starch is a waxy and/or hydrothermally treated
16 starch.

17
18 Preferred features of each aspect of the invention
19 are as for each of the other aspects mutatis
20 mutandis.

21
22 **Detailed description**

23
24 As described above, the present inventors have
25 discovered that existing treatments for conditions
26 characterised by hypoglycaemic episodes may be
27 improved and/or supplemented by the use of waxy
28 starches as sources of α -glucan, thus enabling
29 significant improvement to control over the rate of
30 glucose formation and appearance in the blood
31 mammals. Such starches significantly outperform the
32 conventionally used 'corn starch' (native maize

1 starch) in terms of duration of glucose release due
2 to amylase hydrolysis in the small intestine.

3

4 Moreover, the inventors have shown that the glucose
5 release profile may be further dramatically
6 prolonged by modifications to the optimised starch
7 e.g. by hydrothermal treatment for example, by heat
8 moisture treatment. Indeed, hydrothermal treatment
9 also provides considerable improvement in
10 conventional non-waxy starches. Thus, the invention
11 also extends to the methods of the first, second and
12 third aspect of the invention, wherein the waxy
13 starch is substituted by any hydrothermally treated
14 starch, preferably heat moisture treated starch
15 (whether waxy or non-waxy).

16

17 *Starches*

18

19 Starches are produced by plants as roughly spherical
20 granules ranging in diameter from <5 to >50 μ m.
21 Depending on source they contain ~11-17% moisture,
22 ~82-88% α -glucan, <~1.5% lipid and <~0.6% protein.
23 The α -glucan comprises two types of molecules:
24 amylose and amylopectin. The former is an
25 essentially linear molecule comprising about 99% α -
26 (1-4) and about 1% α -(1-6) bonds with a molecular
27 weight of ~500,000. Amylopectin is much bigger than
28 amylose with a molecular weight of a few million and
29 is heavily branched with ~95% α -(1-4) and ~5% α -(1-
30 6) bonds. The exterior chains of amylopectin
31 associate together as double helices which

1 themselves register together to form crystalline
2 laminates. These crystalline laminates are
3 interspersed with amorphous material comprising non-
4 crystalline (branched regions) of amylopectin plus
5 amylose. The amylose may form inclusion complexes in
6 cereal starches with lipids causing the presence of
7 two forms of the molecule: lipid complexed and lipid
8 free.

9
10 In normal starches, amylopectin is the 'seat' of
11 crystallinity. Waxy starches have a greater
12 proportion of crystallinity due to the higher
13 amylopectin content. High amylose starches contain
14 both amylopectin and amylose generated crystalline
15 material.

16
17 Starches containing <~20% amylose (80% amylopectin)
18 are commonly referred to as 'waxy', ~20-40% are
19 commonly referred to as 'normal' and ~>40% are
20 commonly referred to as high amylose or amylo-
21 starches. Normal maize and wheat starches are, for
22 example, ~30% amylose.

23
24 The semi-crystalline native starch granules are
25 insoluble and largely indigestible by man's
26 digestive enzymes. The control of native starch
27 digestion in man is not well understood although it
28 does not provide a major nutritional focus as most
29 starches are processed prior to cooking. Processing
30 of starch incorporates cooking in water which
31 disrupts the crystalline regions and 'gelatinises'
32 the starch. Gelatinised starches are very digestible

1 because of their amorphous nature by amylases and
2 related enzymes in the small intestine of man.
3 Native and resistant starches (see below), although
4 in part digested in the small intestine, are
5 fermented in the colon. Products of carbohydrate
6 fermentation in the colon include short chain fatty
7 acids (SCFAs) and gasses like carbon dioxide,
8 hydrogen and methane.

9
10 Resistant starch takes a number of forms and simply
11 resists hydrolysis by enzymes synthesised in the
12 small intestine of man. This includes: small food
13 particles entrapping starch; native starch;
14 recrystallised (retrograded) starch and; chemically
15 modified starch.

16
17 If starches are hydrolysed (typically chemically
18 with acids or enzymatically with α -amylase and
19 amyloglucosidase) smaller molecules called
20 'dextrins' are generated. Products may be as small
21 as the smallest possible monosaccharide glucose or
22 be slightly hydrolysed but still polymeric. Glucose
23 syrups are made from starch hydrolysis and contain
24 variable proportions of sugars and dextrins
25 depending on the nature and extent of conversion.
26 The extent of conversion is usually defined as
27 dextrose equivalence (DE) which equates reducing
28 power of the hydrolysate to that of pure dextrose
29 (glucose).

30
31 Maltodextrins are DP20 or less, GRAS quality,
32 tasteless and very soluble. They are easily

1 digestible and are used in energy drinks because of
2 their solubility and reportedly relatively slow
3 digestibility compared to glucose (which is simply
4 absorbed). The difference in rate of glucose
5 appearance in the blood as a consequence of drinking
6 glucose or maltodextrin solutions is relatively
7 small (e.g. ~45minutes) because of the extent of
8 conversion of the maltodextrin.

9
10 In the present invention, any suitable semi-
11 crystalline or crystalline starch may be used. In
12 preferred embodiments, the starch of and for use in
13 the invention is a waxy starch.

14
15 The starch may be a naturally produced starch or may
16 be synthetically produced using any suitable method
17 e.g. plant breeding or biotechnological methods
18 (including transgenic technology etc.).

19
20 Preferred native starches are waxy with an average
21 diameter of approximately 15-35 μ m.

22 23 24 **Hydrothermally Treated Starch**

25
26 As discussed above and shown in the examples below,
27 the inventors have found that particularly good
28 results are obtained when using hydrothermally
29 treated starch.

30
31 Two main methods are currently used for the
32 hydrothermal treatment of starch: heat-moisture

1 treatment (high temperature, low moisture) and
2 annealing (high moisture, low temperature).
3

4 **Heat Moisture Treated Starch (HMT Starch)**

5
6 Heat and moisture treated starch is typically
7 produced by exposing moist starch (e.g. 15-30%
8 moisture) to temperatures of e.g. 95°C to 130° for
9 periods up to 30 hours (typically 16-24). These
10 ranges do not exclude other heat-moisture profiles.
11 For example, HMT starch for use in the invention may
12 be produced by thermally treating starch in a sealed
13 container under the following conditions: 20%
14 moisture and 105°C for 16 hours. The treated starch
15 may then be cooled to room temperature, air-dried
16 and then passed through 300um sieve.
17

18 Such heat moisture treatment results in a number of
19 significant property changes to starches. The extent
20 of the effect varies with the type of starch but in
21 general the effects are:
22

- 23 • increased gelatinisation temperature
 - 24 • reduced water absorption and swelling power
 - 25 • changed X-ray diffraction pattern
 - 26 • increased enzyme susceptibility
- 27

28 As described herein, although heat moisture
29 treatment results in starches having increased
30 susceptibility to enzymatic degradation, the
31 inventors have surprisingly shown that when used in
32 methods of the invention, heat moisture treated

1 starches provide significantly greater prolongation
2 of the time period over which serum glucose levels
3 are maintained compared to the corresponding non
4 heat moisture treated starches.

5

6 **Annealing Treatment of Starch**

7

8 In certain embodiments of the invention the starch
9 of and for use in the invention is annealing treated
10 starch. Any suitable annealing treated starch may
11 be used.

12

13 Annealing is a process in which starch granules are
14 treated for a relatively long time in excess amounts
15 of water at a temperature slightly higher than room
16 temperature. Typically, annealing of starch
17 involves incubation of starch granules in water
18 (>40% w/w), for a time period in the range 1 hour to
19 10 days at a temperature between the glass
20 transition and the gelatinisation temperature.
21 Preferred annealing conditions are less than 10°C
22 below the onset of gelatinisation temperature, in
23 excess water for up to 7 days.

24

25 **Treatment/Therapy**

26

27 "Treatment" (which, unless the context demands
28 otherwise, is used interchangeably with "therapy",
29 includes any regime that can benefit a human or non-
30 human animal. The treatment may be in respect of an
31 existing condition or may be prophylactic

1 (preventative treatment). Treatment may include
2 curative, alleviation or prophylactic effects.

3

4 **Food Compositions**

5

6 The invention extends to a therapeutic food
7 composition for the treatment of diseases
8 characterised by hypoglycaemic episodes, wherein
9 said composition comprises a semi-crystalline
10 starch.

11

12 The therapeutic food compositions of and for use in
13 the present invention may consist solely of said
14 starches or preferably may comprise further
15 additives. Such additives may contribute merely to
16 the palatability of the composition, e.g.
17 flavourings, or may contribute significant calorific
18 value, for example, sugars with a more rapid release
19 profile than the starches, or lipids. These
20 compounds may be incorporated to slow gastric
21 emptying and facilitate the effect (e.g. amino
22 acids, lipids etc.).

23

24 The therapeutic food composition can take a variety
25 of forms, for example as a food, a food supplement,
26 a liquid, an emulsion or mixture thereof.

27 Preferably, it is prepared as a ready to eat
28 foodstuff, for example as a snackbar, a baked
29 product, pasta or drink.

30

31 Alternatively, the therapeutic food composition may
32 be administered as a pharmaceutical composition,

1 which will generally comprise a suitable
2 pharmaceutical excipient, diluent or carrier
3 selected dependent on the intended route of
4 administration.

5
6 Some suitable routes of administration include (but
7 are not limited to) oral, rectal or parenteral
8 (including subcutaneous, intramuscular, intravenous,
9 intra dermal) administration.

10
11 For intravenous injection the active ingredient will
12 be in the form of a parenterally acceptable aqueous
13 solution which is pyrogen-free and has suitable pH,
14 isotonicity and stability. Those of relevant skill
15 in the art are well able to prepare suitable
16 solutions using, for example, isotonic vehicles such
17 as Sodium Chloride Injection, Ringer's Injection,
18 Lactated Ringer's Injection. Preservatives,
19 stabilisers, buffers, antioxidants and/or other
20 additives may be included, as required.

21
22 However, the composition is preferably for
23 administration orally. Pharmaceutical compositions
24 for oral administration may be in tablet, capsule,
25 powder or liquid form. A tablet may comprise a
26 solid carrier such as gelatin or an adjuvant.
27 Liquid pharmaceutical compositions generally
28 comprise a liquid carrier such as water, petroleum,
29 animal or vegetable oils, mineral oil or synthetic
30 oil. Physiological saline solution, dextrose or
31 other saccharide solution or glycols such as

1 ethylene glycol, propylene glycol or polyethylene
2 glycol may be included.

3

4 Examples of the techniques and protocols mentioned
5 above and other techniques and protocols which may
6 be used in accordance with the invention can be
7 found in Remington's Pharmaceutical Sciences, 16th
8 edition, Oslo, A. (ed), 1980.

9

10 **Dose**

11

12 The therapeutic food compositions of and for use in
13 the invention are preferably administered to an
14 individual in a "therapeutically effective amount",
15 this being sufficient to show benefit to the
16 individual. The actual amount administered, and
17 rate and time-course of administration, will depend
18 on the nature and severity of what is being treated.
19 Prescription of treatment, e.g. decisions on dosage
20 etc, is ultimately within the responsibility and at
21 the discretion of general practitioners and other
22 medical doctors, and typically takes account of the
23 disorder to be treated, the condition of the
24 individual patient, the site of delivery, the method
25 of administration and other factors known to
26 practitioners.

27

28 The optimal dose can be determined by physicians
29 based on a number of parameters including, for
30 example, age, sex, weight, severity of the condition
31 being treated, the active ingredient being
32 administered and the route of administration.

1

2

3 The invention will now be described further in the
4 following non-limiting examples. Reference is made
5 to the accompanying drawings in which:

6

7 Figure 1 shows schematically glucose and glycogen
8 metabolism reactions.

9

10 Figure 2 shows a comparison of the hydrolysis
11 profile of native starches using the Karkalas et al
12 (1992) procedure;

13

14 Figure 3 shows blood glucose level after consumption
15 of native starches;

16

17 Figure 4 shows a comparison of the blood lactate
18 level after consumption of native starches;

19

20 Figure 5 shows a comparison of blood glucose after
21 consumption of two native starches (wheat and waxy
22 maize) with added pregelatinised (maize) starch;

23

24 Figure 6 shows a comparison of the blood lactate
25 level after consumption of two native starches
26 (wheat and waxy maize) with added pregelatinised
27 (maize) starch;

28

29 Figure 7 shows a comparison of blood glucose after
30 consumption of starch (native waxy maize and
31 soluble) encapsulated with pectin and alginate.

32

1 Figure 8 shows a comparison of blood lactate after
2 consumption of starch (native waxy maize and
3 soluble) encapsulated with pectin or alginate.

4

5 Figure 9 shows a comparison of blood glucose after
6 consumption of starch (native waxy maize, soluble)
7 encapsulated with lipid.

8

9 Figure 10 shows a comparison of blood glucose after
10 consumption of heat-moisture treated waxy maize
11 starch, waxy maize and normal maize starch.

12

13 Figure 11 shows a comparison of blood lactate after
14 consumption of heat-moisture treated waxy maize
15 starch, waxy maize and normal maize starch.

16

17 Figure 12 shows a comparison of digestibility of
18 native and heat-moisture treated waxy maize
19 starches.

20

21 Figure 13 shows a comparison of digestibility of
22 native and heat-moisture treated normal maize
23 starches.

24

25 **Example 1: In vitro hydrolysis**

26

27 Common native starches (barley, maize, potato, rice
28 and wheat) were evaluated using the Karkalas *et al*
29 (1992) (*in vitro*) method to identify their amylase
30 hydrolysis profile and potential for slow release of
31 energy in individuals. These data are presented in
32 Figure 2.

1
2 As can be seen from Figure 2 that rice starch has a
3 fast energy release profile initially followed by a
4 much slower process. In contrast, potato and high
5 amylose starches show great resistance towards
6 amylase hydrolysis and are nearly untouched by the
7 enzyme. Starches from normal maize, waxy maize and
8 wheat show continuous slow release energy profile.
9 These data provide the basis for an *in vitro*
10 selection of the most appropriate starch for this
11 purpose (as discussed later). Note that they do not
12 define the rate or extent of hydrolysis in the
13 actual gut but provide a means of *ordering* the rate
14 of extent of hydrolysis based on the *in vitro*
15 system.

16

17 **Example 2: Digestion of native starches**

18

19 Under clinical supervision, individuals suffering
20 from GSD were fed 60g samples of native starches
21 dispersed in semi-skimmed milk. The amount of blood
22 glucose and lactate were monitored and are presented
23 in Figures 3 and 4. Native potato starch was not
24 consumed in view of its resistance to digestion (and
25 cause of potential colonic disturbance accordingly).

26

27 These data show that waxy rice starch released
28 glucose very quickly where the highest (too high)
29 initial glucose peak (8.7 mmol l^{-1}) at 1 hour post
30 ingestion was obtained. The blood glucose level then
31 dropped to 3 mmol l^{-1} within 4.5 hours (270 minutes).
32 Normal rice showed a much lower initial glucose peak

1 with a longer release profile corresponding to
2 3.2mmol l^{-1} within 5 hours (300 minutes) but less
3 glucose released in the time course of the
4 experiment compared to the waxy rice starch. High
5 amylose starch too extensively restricted glucose
6 release (although this could be moderated by
7 physical/ chemical/ enzymatic or biotechnological
8 modification). The normal maize starch ('corn
9 starch') exhibited a low glucose peak 1 hour
10 (6.6mmol l^{-1}) after ingestion with an extended release
11 of 2.9mmol l^{-1} after 300 minutes. The waxy maize
12 starch surprisingly showed the optimal release
13 profile with less than 7mmol l^{-1} blood glucose 1 hour
14 post ingestion, a significant glucose release
15 profile for up to 6 hours (330 minutes) which
16 dropped to 2.9mmol l^{-1} at this point.

17
18 Lactate in the blood also reflected the starch
19 consumed (Figure 4). The high amylose maize starch
20 provided the least lactate response (highest
21 lactate) as it was little digested (Figure 3). The
22 greatest reduction in lactate was achieved by the
23 waxy maize starch and in common with the previous
24 data promotes its potential use for GSD and similar
25 conditions requiring slow release of energy.

26
27 Based on these data, there is clearly a granule size
28 and compositional effect that regulates native
29 starch hydrolysis to glucose in the gut. There is a
30 balance between choosing a starch for therapy based
31 on the 1 hour glucose peak, duration of release and

1 the amount (integrated area) of glucose release with
2 time. A preferred starch for the purpose, therefore:

3
4 a) is highly crystalline (semi-crystalline) with
5 waxy starches providing the most appropriate
6 crystalline (amylopectin) matrices for this purpose.

7
8 b) has reasonably large granules without exceeding
9 the digestive capacity. Rice starches (~5µm diameter
10 on average) are too small. Maize starch granules are
11 preferred (~20-25µm diameter on average).

12
13 It is recognised that the cereal starches contain
14 lipid and that other starches may be more
15 appropriate in terms of size and composition.
16 However, in view of the lack of digestibility and
17 potential dangers of eating large granules (which
18 may cause colonic lesions) it is proposed that
19 granules in excess of ~40µm diameter are not
20 consumed for this purpose.

21
22 **Example 3: Digestion of native starches in the**
23 **presence of a pre-gelatinised starch thickener**

24
25 Under clinical supervision, individuals suffering
26 from GSD were fed 60g samples of two native starches
27 (wheat or waxy maize), each sample containing 54g of
28 either starch and 6g pregelatinised maize starch
29 (National B37, National Starch & Chemical) dispersed
30 in cold semi-skimmed milk. The amount of blood
31 glucose and lactate were monitored and are presented
32 in Figures 5 and 6.

1
2 These data show that even in the presence of
3 amorphous (pre-gelatinised) starch the waxy maize
4 starch resists digestion (Figure 5) more than the
5 wheat starch, which contains a bi-modal distribution
6 of small (~10µm average diameter) and large (~25µm
7 average diameter) granules but with similar
8 composition (amylose, lipid, moisture and protein).
9 This is reflected in a lower blood lactate (even
10 though the patients started with a higher lactate
11 content when presented with the waxy maize starch
12 (as shown in Figure 6). The importance of this work
13 is that it shows that even if the waxy starch is
14 mixed with other materials that have the capacity to
15 provide a quicker glucose response it can still
16 provide a slow release function.

17
18 **Example 4: Digestion of native starches in the**
19 **presence of non-starch polysaccharides**

20
21 Native waxy maize starch (Amioca Powder T, National
22 Starch) was encapsulated in soluble starch (Crystal
23 Tex 626, National Starch) and pectin (LM-104AS-FS,
24 CPKelco) or alginic acid (Manugel GMB, Manugel)
25 according to Tester and Karkalas (1999). The final
26 starch to non-starch polysaccharide (NSP) ratio was
27 5.7:1 or 19:1. The proportion of the soluble starch
28 to native starch varied according to the proportion
29 of native starch used for the two conditions but was
30 the same for both non-starch polysaccharide
31 conditions and simply serves as a comparison.

1 Under clinical supervision, individuals suffering
2 from GSD were fed 70g or 63g (depends on the starch
3 to NSP ratio) samples of NSP encapsulated starch
4 dispersed in cold semi-skimmed milk. The amount of
5 blood glucose and lactate were monitored and are
6 presented in Figures 7 and 8.

7
8 These data show that, although the amount of starch
9 modifies the extent of glucose release as expected,
10 the alginate or pectin components do not stretch out
11 the release profile much beyond 5 hours (300
12 minutes). Hence, the presence of a non-starch
13 polysaccharide 'raft' or food matrix is not enough
14 in itself to slow the rate of starch hydrolysis
15 accordingly (whether native or soluble). The blood
16 lactate response reflects the blood glucose where
17 alginate appears to reduce lactate production more
18 markedly than pectin (since it restricts hydrolysis
19 more).

20

21 **Example 5: Digestion of native starches in the**
22 **presence of lipid**

23

24 Starch (Amioca Powder T, National Starch) with or
25 without addition of soluble starch (Crystal Tex 626,
26 National Starch) was encapsulated in lipid (Revel A,
27 Loders Croklaan B. V.) as follows. The lipid was
28 dissolved in the minimal amount of ethanol possible
29 to dissolve the starch. The starch was then
30 thoroughly mixed with the ethanol solution until
31 homogeneous. The starch was laid on a tray and air
32 at 35°C was allowed to flow over the

1 ethanol/lipid/starch system (in a fume cupboard)
2 until the ethanol had all evaporated from the
3 system. The final starch to lipid ratio was 9:1.
4 When used, the proportion of soluble starch was 10%
5 of the total starch fraction.

6
7 Under clinical supervision, individuals suffering
8 from GSD were fed 66g samples of lipid encapsulated
9 starch dispersed in cold semi-skimmed milk. The
10 amount of blood glucose was monitored and is
11 presented in Figures 9.

12
13 These data show that the lipid restricts the amount
14 of starch digestion at all times (see previous
15 figures for comparison). Overall, this approach is
16 not appropriate for the control of glucose release
17 (extent of hydrolysis) from the starch as the amount
18 released over time and the actual duration is
19 reduced.

20
21 **Example 6: Digestion of hydrothermally treated**
22 **starches.**

23
24 Starch (Amioca Powder T, National Starch) was
25 thermally treated in a sealed container under the
26 following conditions: 20% moisture and 105°C for 16
27 hours. The treated starches were then cooled to room
28 temperature, air-dried and then passed through 300µm
29 sieve.

30
31 Under clinical supervision, individuals suffering
32 from GSD were fed 60g or 90g samples of heat-

1 moisture treated starch dispersed in cold semi-
2 skimmed milk. The amount of blood glucose and
3 lactate were monitored and are presented in Figures
4 10 and 11.

5

6 These data show that:

7

8 (i) Heat moisture treated (HMT) waxy maize starch
9 has a much reduced initial glucose response at
10 60 minutes than native waxy maize starch
11 (Figure 10).

12 (ii) Because of the reduced initial response more
13 can be fed to be within acceptable levels of
14 glucose increase at this time (where a
15 preferred response is $<8\text{mmol l}^{-1}$).

16 (iii) As a consequence of the above, greater
17 amounts could be fed (90g versus 60g) leading
18 to 7.5 hour (450 minutes) profile where the HMT
19 starch can still maintain the blood glucose at
20 $\sim 2.5\text{mmol l}^{-1}$.

21 (iv) The glucose response provides an acceptable
22 and desirable lactate response accordingly
23 (Figure 11).

24

25 Similar results were obtained when repeating the
26 experiments on further patients (results not shown).

27

28 These data are reinforced by the in vitro assay as
29 shown in Figure 12. Here the HMT treatment can be
30 shown to clearly restrict the hydrolysis of the waxy
31 maize starch.

32

1 Hence, the combination of a waxy starch and its heat
2 moisture treatment allows for the formation of a
3 desirable slow release of glucose therapy. The waxy
4 maize starch is potentially more crystalline than
5 normal or high amylose starches in view of the high
6 amylopectin content.

7
8 A particularly preferred type of starch for this
9 purpose is: semi crystalline with, preferably, the
10 highest proportion of crystallinity possible and
11 with amylase accessibility enhanced by the heat
12 moisture processing.

13
14 Moreover, in order to show that the advantages
15 conferred by hydrothermal treatment is not limited
16 to waxy starches, the digestibility of native and
17 heat-moisture treated normal maize starch was tested
18 using the same assay as in Figure 12. The results
19 are shown in Figure 13. As shown in Figure 13,
20 hydrothermal treatment of normal maize starch (i.e.
21 non-waxy starch) improves the hydrolysis profile of
22 the starch. Thus, the results support the use of
23 hydrothermally treated normal starch for slow
24 release glucose therapy in the methods of the
25 invention.

26
27 All documents referred to in this specification are
28 herein incorporated by reference. Various
29 modifications and variations to the described
30 embodiments of the inventions will be apparent to
31 those skilled in the art without departing from the
32 scope and spirit of the invention. Although the

1 invention has been described in connection with
2 specific preferred embodiments, it should be
3 understood that the invention as claimed should not
4 be unduly limited to such specific embodiments.
5 Indeed, various modifications of the described modes
6 of carrying out the invention which are obvious to
7 those skilled in the art are intended to be covered
8 by the present invention.

9
10

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